Conferences and Reviews

Controversies in Patient Selection for Liver Transplantation

EMMET B. KEEFFE, MD, *and* CARLOS O. ESQUIVEL, MD, PhD, *San Francisco, California*

A variety of specific conditions often stimulate controversy regarding candidacy for liver transplantation. We review the published experience with liver transplantation for alcoholic liver disease, fulminant and chronic hepatitis B, and hepatocellular carcinoma and transplantation in older subjects. Liver transplantation for alcoholic liver disease and in subjects older than 60 years is becoming less controversial because recent data demonstrate that these patients have excellent survival and good quality of life after transplantation. Only 10% to 15% of persons with alcoholism return to drinking after transplantation, and most do so only transiently. Liver transplantation for patients with hepatitis B virus infection or primary liver cancer is more problematic because recurrent disease is common in both conditions. After transplantation for chronic hepatitis B, 80% to 90% of patients have reinfection of the allograft and long-term survival is 45% to 50%. Patients receiving transplants for hepatocellular carcinoma have only 20% to 30% long-term survival, but these survivors are cured of malignancy. Data are presented to support continued liver transplantation for chronic hepatitis B and hepatocellular carcinoma; however, patients must be selected based on factors that predict a favorable outcome, and experimental therapies should be employed to explore ways to improve the existing survival rates.

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Human orthotopic liver transplantation was initiated in 1963, but results were poor until the early 1980s when the one-year survival rate increased from approximately 30% to more than 60%.[1] Several factors, including the refinement of surgical techniques, improved perioperative care, more effective and safer immunosuppressive therapy, and better selection of patients, accounted for this remarkable increase in survival. In 1983 the treatment of end-stage liver disease with orthotopic liver transplantation was declared no longer experimental.[2] The survival of patients undergoing the procedure has improved progressively throughout the 1980s and early 1990s. Survival rates greater than 80% are now routine at transplant centers, as evidenced by 87% one-year survival and 85% two-year survival at California Pacific Medical Center (CPMC) during the first one to two years of the liver transplantation program.[3,4]

Over the past decade, the number of liver transplant operations and centers has grown dramatically. More than 100 centers are now operating in the United States, and approximately 3,000 liver transplantations were performed in 1992. This growth, fueled further in 1991 by the approval of Medicare funding for the operation, has resulted in an increase in the number of patients on transplant waiting lists and the number of deaths before transplantation can be achieved. These factors present many challenges for the future, including the refinement of patient selection criteria.[5] The merits of performing transplants in certain patient groups, specifically those with underlying diseases that may recur after the procedure, continue to be controversial.

The classic indications for orthotopic liver transplantation are advanced cirrhosis, fulminant hepatic failure, unresectable hepatic cancer, and metabolic liver disease.[1] These broad indications encompass nearly all types of liver disease. In addition, patients must have no alternative therapy, no contraindications to transplantation, and the ability to pay for the procedure and follow-up care. Absolute contraindications include the acquired immunodeficiency syndrome; primary hepatic malignancy spread beyond the liver; active and untreatable alcoholism or drug abuse; advanced extrahepatic disease, particularly cardiopulmonary conditions; and thrombosis of the splanchnic venous circulation (portal, splenic, and superior mesenteric veins).

Within these broad selection criteria for liver transplantation, controversy exists regarding whether patients with certain liver diseases should be approved for the procedure. For example, should patients with alcoholic cirrhosis, chronic hepatitis B, or primary liver cancer (hepatocellular carcinoma or cholangiocarcinoma) receive transplants? These three conditions share several features—in particular the possibility of recurrence and reduced long-term survival after transplantation—that

From the Department of Transplantation, California Pacific Medical Center, San Francisco.
Reprint requests to Emmet B. Keeffe, MD, California Pacific Medical Center, 2340 Clay St, Suite 423, San Francisco, CA 94115.

ABBREVIATIONS USED IN TEXT

CPMC = California Pacific Medical Center
CT = computed tomographic
HBeAg = hepatitis B e antigen
HBIG = hepatitis B immune globulin
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HDV = hepatitis delta virus
TNM = tumor-node-metastasis

account in part for their controversial status. Because donor organs are in short supply and the number of deaths on the waiting list has increased, the argument is presented that donor organs might better be allocated to persons on the waiting list expected to have optimal initial and long-term survival. Another area that often stimulates debate regarding candidacy for the procedure is the presence of associated medical conditions that may adversely influence the outcome. For example, should patients who are older than age 60 receive transplants? These four areas of controversy will be reviewed.

Alcoholic Cirrhosis

Until the past few years, orthotopic liver transplantation was not considered a treatment option for patients with alcoholic liver disease. The initial experience with transplantation for these patients at several transplant centers demonstrated poor results, and there was concern that a high recidivism rate would substantially reduce long-term survival. In 1988, researchers from the University of Pittsburgh found that the survival of 42 patients who received transplants for alcoholic liver disease was not different from the survival of patients undergoing the procedure for other causes of cirrhosis.[6] Moreover, only 2 of 35 patients surviving more than six months returned to alcohol abuse.

Many compelling reasons exist for patients with alcoholic cirrhosis to be considered for liver transplantation. Alcoholic liver disease is prevalent and often fatal, with more than 30,000 liver-related deaths annually in the United States associated with alcoholism.[7] Alcoholic cirrhosis is the cause of more than half of the cases of end-stage liver disease in the United States. Patients undergoing transplantation for alcoholic cirrhosis are often younger than 50. Thus, the potential exists for long-term survival and a return to productivity in the home and workplace. Most important, the published survival data from several liver transplant centers have confirmed the findings of the 1988 University of Pittsburgh report and demonstrated that the long-term survival for patients with alcoholic cirrhosis after the procedure matches the survival of patients with other types of cirrhosis.[8-10] Finally, after transplantation the rate of recidivism is low, averaging 10% to 12%, and the rate of compliance with medical follow-up by patients with alcoholism is high.[9-11]

Liver transplant centers have applied different selection criteria for patients with alcoholic liver disease. The development of a rational and structured approach that predicts compliance and long-term sobriety in the post-transplantation period is critically important and has been reported by some centers.[9,10] A multidisciplinary team of medical, surgical, and psychiatric members contributes to pretransplant evaluation and the determination of suitability for transplantation. Investigators from the University of Michigan developed an "alcoholism prognosis scale" based on the acceptance of alcoholism by the patient and family, social functioning and stability, and changes in life-style such as substitute activities, social relationships, and hope and self-esteem.[9] Of all patients with alcoholic cirrhosis referred to the University of Michigan for liver transplantation, fewer than 50% were accepted.[9] The actuarial survival of those patients with alcoholism who received transplants was no different from that of the patients without alcoholism; both had survival of about 80%. Only a small number of alcoholic patients drank after receiving a transplant, and most of these only transiently. These investigators attributed their center's success with liver transplantation for alcoholic cirrhosis to the use of their alcoholism prognosis scale.

Using a slightly different but conceptually similar approach at CPMC, the results of transplantation for alcoholic cirrhosis have also been good with a 93% actuarial survival at 42 months.[10] Based on their psychosocial state and medical condition, referred patients with alcoholic liver disease are categorized by a standardized protocol into groups with low risk, moderate risk, and high risk for recidivism and noncompliance. Low-risk patients admit alcoholism, agree to participate in an alcohol treatment program, sign an alcohol treatment contract, have not failed treatment programs in the past, do not have major psychiatric disease, and are medically fit. These low-risk patients are placed on the waiting list for transplantation. High-risk patients have failed alcohol rehabilitation programs, deny their alcoholism, refuse to sign an alcohol contract, have major psychiatric disease, and have advanced coincidental medical problems or alcohol damage to organs other than the liver. These patients are turned down for the procedure. Moderate-risk patients fall between the high- and low-risk groups and are deferred for transplantation. These patients are observed by the referring physician and the transplant team while they participate in an alcohol treatment program; if they are compliant and remain abstinent, they are subsequently placed on the waiting list for the procedure. Follow-up results of the initial 47 patients entered into this prospective protocol have confirmed its predictive value. Of 31 low-risk patients, 27 received transplants; 5 of the 31 patients (16%) drank alcohol, but only transiently. Ten patients were classified as moderate risk and deferred, and two of these patients later received transplants; all ten patients either were noncompliant or drank alcohol. Of the six patients classified as high risk, five (83%) were noncompliant or drank alcohol. In fact, the actuarial survival of patients undergoing transplantation for alcoholic cirrhosis at CPMC is better than that of patients who receive transplants for other conditions at our institution (Figure 1).

The period of abstinence required to be considered for liver transplantation has changed dramatically in recent

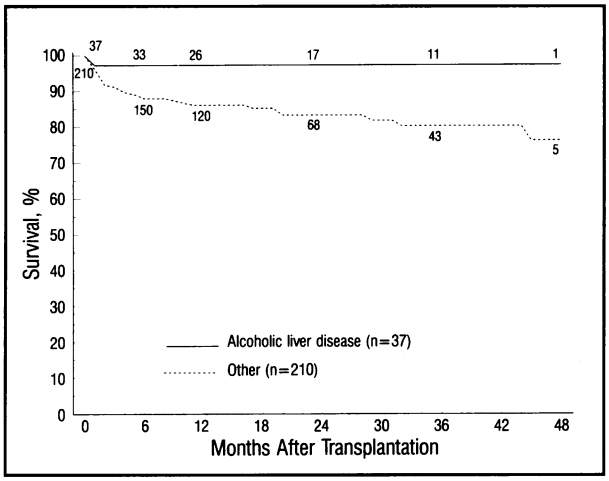

Figure 1.—The actuarial survival of patients undergoing orthotopic liver transplantation for alcoholic cirrhosis surpasses that of patients who receive transplants for other indications at California Pacific Medical Center.

years. Many transplant programs previously mandated six months of abstinence, but many patients died of liver failure during that arbitrary and fixed waiting period. Some period of abstinence is still an important consideration in predicting posttransplant sobriety, but it is no longer the sole determining factor and is considered along with other predictors of abstinence.[9,10] Because patients with acute alcoholic hepatitis are typically drinking alcohol up to or near the time of hospital admission, they are usually not offered transplantation.

In summary, alcoholic cirrhosis is becoming less of a controversial issue in patient selection for orthotopic liver transplantation, although the topic continues to be debated.[12-14] Medicare recently approved funding for liver transplantation for alcoholic cirrhosis, which has become the single leading indication for the procedure.[14] Alcoholic patients undergoing transplantation should have prognostic factors that predict long-term sobriety and compliance. Survival after the procedure is good (75% to 80%), and most patients (85% to 90%) remain abstinent from alcohol. It is important to note that, although results are currently encouraging, alcoholic patients receiving transplants are highly selected, and follow-up is still relatively short.

Fulminant and Chronic Hepatitis B

A second major area of controversy in selecting patients for orthotopic liver transplantation is whether to offer transplants to patients with hepatitis B virus (HBV) infection. Transplantation for fulminant hepatitis B is associated with good survival and outcome; many of these patients do not have recurrent HBV infection, possibly because a vigorous immune response clears the virus.[15-19] By contrast, the three- to five-year actuarial survival of patients receiving transplants for chronic hepatitis B is 45% to 50%, which is 25% lower than the expected survival after liver transplantation for other causes of end-stage cirrhosis.[1,15,16]

This reduced survival for patients with HBV infection is related to reinfection of the graft, which is often associated with accelerated liver disease and may evolve rapidly to graft failure in some patients.[15,16,20,21] Graft failure, characterized clinically by progressive hyperbilirubinemia and only a modest elevation of aminotransferase levels, has been called "fibrosing cholestatic hepatitis"[20] or "fibrosing cytolytic hepatitis."[21] The histologic findings include a ballooning degeneration of hepatocytes, periportal fibrosis, and a paucity of inflammatory infiltrates.[20,21] These features are accompanied by a prominent expression of hepatitis B surface antigen (HBsAg) and hepatitis B core antigen in most hepatocytes by immunohistochemical staining.[20-23] This enhanced expression of HBV proteins and the lack of significant histologic inflammatory response supports a cytopathogenic role for the virus in this disease after transplantation.[20,21] The precise mechanisms for this direct cytopathogenicity, in contrast to the usual immune pathogenesis of chronic hepatitis B in patients not receiving transplants, is unknown.

Recurrent HBV infection is associated with a broad disease spectrum ranging from an asymptomatic patient with histologic findings of mild focal hepatitis or chronic active hepatitis to a symptomatic patient with chronic active hepatitis with cirrhosis or fibrosing cytolytic hepatitis.[16,20] The recurrence of HBV infection follows the course of the original disease over a variable but accelerated time frame. Even primary hepatocellular carcinoma has been reported after transplantation for chronic hepatitis B.[24] Investigators from King's College in London have identified three phases of recurrent HBV infection after liver transplantation: an incubation phase during which HBsAg is not present or present at decreasing levels; an early infection phase during the first three months after the return of HBsAg positivity; and an established infection phase with a plateau of HBsAg titers and ongoing viral replication with hepatitis B e antigen (HBeAg) or HBV DNA seropositivity or both.[20]

The strongest predictor of the recurrence of HBV infection is the presence of HBV replication as defined by circulating HBeAg or HBV DNA.[16,17] Todo and colleagues reported that only patients who were HBeAg-negative before the transplantation cleared HBV after the procedure.[16] In the overall analysis of their experience, 8 of 30 HBeAg-negative patients cleared the virus, whereas none of 26 HBeAg-positive patients cleared HBsAg. This observation was confirmed by Samuel and associates, who found that patients with chronic hepatitis B with detectable serum HBV DNA had a much greater risk of HBsAg recurrence than patients who were HBV DNA-negative (96% versus 29% at two years).[17] In their institution, all patients received a hepatitis B immune globulin (HBIG) preparation, which reduced HBV reinfection and improved survival in patients without evidence of active HBV replication before transplantation when compared with other series and with their own institutional experience before the initiation of HBIG therapy.

Hepatitis B virus DNA was also an important marker of recurrent HBsAg in a treatment trial in Hannover, Ger-

many, where HBIG was used for patients who received transplants for chronic hepatitis B.[25] Recurrent HBV infection was prevented in only one of nine patients with HBV DNA, HBeAg, or both detected in serum before the transplant. By contrast, HBV recurrence was prevented in 10 of 14 HBV DNA–negative patients. These studies suggest that the degree of viral replication is the major determinant of the incidence and severity of recurrent HBV infection after liver transplantation. Immunosuppressive drugs may play a critical role in HBV replication after transplantation, based on the modulating effects of corticosteroids on HBV replication.[26]

Other factors may influence the recurrence of HBV infection after transplantation. The replication of HBV has been demonstrated in extrahepatic sites such as bone marrow, spleen, and pancreas.[27] Moreover, HBV has been found in peripheral blood mononuclear cells in the absence of hepatic infection after liver transplantation.[28] Another factor that may influence the recurrence of HBV infection is coexistent hepatitis delta virus (HDV) infection.[29-31] Superimposed HDV infection inhibits HBV replication and may enhance the clearance of HBsAg after transplantation. In the study of Todo and co-workers, four of eight anti-HDV–positive patients cleared HBsAg.[16] A survival rate of 78% was reported in 27 HDV-positive patients who received transplants in Italy and Belgium,[30] and 13 of 16 HDV-positive transplant recipients treated with HBIG in France have remained HBsAg-negative.[31]

In a review of the cumulative experience from the University of Pittsburgh with liver transplantation for fulminant and chronic hepatitis B, the long-term survival of transplant recipients surviving more than 60 days was 60% (23 of 38 patients), which is substantially less than the 80% survival reported in a control group receiving transplants for other causes of end-stage liver disease.[16] The actual survival, however, was only 45% of the original 51 patients transplanted for chronic hepatitis B. In contrast, seven of eight patients who received transplants for fulminant hepatitis B survived more than 60 days. One patient cleared HBsAg, and five of the surviving seven had no serious hepatic dysfunction. The treatment of HBV infection was attempted with active and passive immunization. Of 22 patients treated with this regimen and surviving more than 60 days, 6 cleared HBsAg.

At CPMC, 17 patients underwent 19 liver transplant operations for chronic hepatitis B and 5 patients had 6 transplantations for fulminant hepatitis B. The actuarial survival of the 17 patients receiving transplants for chronic hepatitis B was 78%, and all patients receiving transplants for fulminant hepatitis B are alive (Figure 2). Five of seven patients receiving HBIG for three to six months are HBsAg- and HBV DNA-negative; two of these five patients are also anti-HDV–positive. Three of the five patients (60%) receiving transplants for fulminant hepatitis B have recurrent HBV infection.

Various medical therapies have been used singly or in combination to prevent or treat recurrent HBV infection in transplant recipients. Hepatitis B immune globulin appears to show the greatest promise, but data regarding its

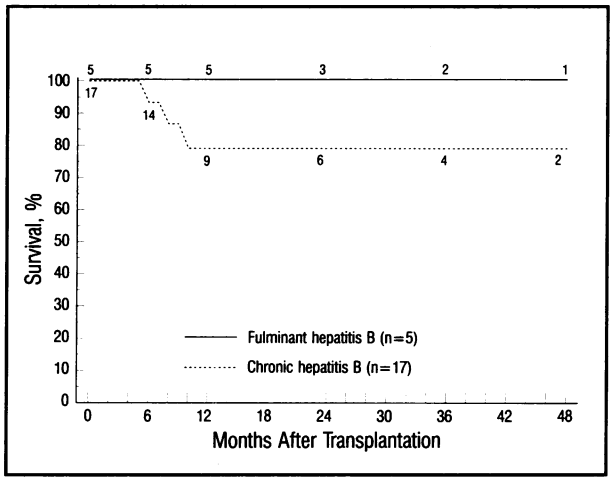

Figure 2.—The actuarial survival of patients undergoing orthotopic liver transplantation for chronic hepatitis B and fulminant hepatitis B at California Pacific Medical Center is shown.

efficacy are conflicting. Moreover, HBIG therapy has a high cost that is typically not reimbursed by insurance programs in the United States. In addition, the commercial products used in Europe may have a different efficacy and side effects compared with the US product, and the US product is not marketed for intravenous use. In research protocols, HBIG is typically given for varying time periods (3 months to 2 years) in intravenous or intramuscular doses to maintain anti-HBs levels greater than 100 units per liter. A French group treated 110 HBsAg-positive patients with long-term HBIG for as long as two years and found that HBsAg reappeared in only 22.7%.[17] The overall two-year actuarial recurrence of HBsAg was 59% after transplantation for chronic hepatitis B, 13% after transplantation for chronic hepatitis B with HDV coinfection, and 0% after the procedure for fulminant hepatitis B. The recurrence rate of HBsAg was 96% in patients with chronic hepatitis B and serum HBV DNA before transplantation versus 29% in those without HBV DNA. In the Hannover study, the infection did not recur in more than 80% of 23 patients treated with long-term HBIG therapy.[25] Reinfection developed in only a minority of patients who were HBV DNA-negative but in all patients who were HBV DNA-positive. At CPMC five of seven patients receiving HBIG for three to six months remain HBsAg- and HBV DNA-negative. In contrast, a recent preliminary report from the University of Nebraska Medical Center found that the use of HBIG was not effective and that only 2 of 11 patients survived long term after transplantation.[32]

Other medical therapies that have been used to prevent or treat HBV reinfection after liver transplantation have not been successful. Active immunization with HBV vaccine and interferon alfa have not been efficacious.[16,33] The use of monoclonal antibodies against HBsAg, rather than the standard polyclonal HBIG, is being studied to determine if this approach will produce higher titers of anti-HBs and less HBV reinfection.[34] Ganciclovir has been reported in preliminary studies to temporarily decrease

serum HBV DNA in patients with chronic hepatitis B after kidney and liver transplantation.[35] The practicality and long-term results of this approach remain uncertain. What is needed is an effective antiviral agent that will eradicate HBV.

In summary, the current approach of many transplant centers is to offer liver transplantation to patients with fulminant and chronic hepatitis B and liver failure, but only when they are entered into an experimental protocol, such as therapy with HBIG. Some centers perform transplantation on patients with chronic hepatitis B only if they are HBV DNA-negative or HBeAg-negative or both. Enough patients survive and return to productive lives to justify the continued use of transplantation for chronic hepatitis B. Unfortunately, patients with end-stage liver disease and HBsAg positivity are excluded by Medicare, some state Medicaid programs, and some private insurance programs from coverage for this procedure. If HBIG or other experimental therapies can reduce or delay HBV reinfection or ameliorate the expression of hepatitis B in the allograft, then even more patients may be able to survive until a specific antiviral agent can be found that permanently suppresses or eradicates HBV.

Another possible alternative is xenotransplantation, as recently demonstrated by the short-term successful transplantation of a baboon liver into a patient with end-stage chronic hepatitis B.[36] This approach is experimental and requires broader study, but xenotransplantation may have particular application in patients with advanced chronic hepatitis B because the baboon liver is resistant to HBV infection.

Hepatocellular Carcinoma

The third major controversial issue of patient selection for orthotopic liver transplantation is primary hepatic carcinoma that is confined to the liver and cannot be resected. In this article, we will focus on hepatocellular carcinoma and will not discuss cholangiocarcinoma, which nearly always recurs, or other benign and malignant tumors of the liver.

Fibrolamellar hepatocellular carcinoma is a clinicopathologic variant that has a more favorable outcome. Pathologists can recognize this variant on the basis of unique histologic features, particularly bands of fibrous tissue. In general, it grows more slowly than other hepatocellular carcinomas and has a high resectability rate.[37,38] Compared with patients who had other liver cancers (n = 64), patients with fibrolamellar hepatic carcinoma (n = 12) who underwent subtotal hepatic resection at the University of Pittsburgh had a significantly better survival rate at 5 years (64.8% versus 26.3%).[38] On the other hand, the five-year survival rate of patients with standard and fibrolamellar hepatocellular carcinoma was not different after transplantation (37.5% versus 36.5%).[38] The rest of this review will focus on nonfibrolamellar hepatocellular carcinoma.

The selection of patients with hepatic cancer for transplantation is dependent on several factors. The malignant lesion must be confined to the liver as documented preoperatively by abdominal, pelvic, and chest computed tomographic (CT) scans and a bone scan. A specific indication for transplantation in patients with hepatocellular carcinoma is poor hepatic function due to coexistent advanced cirrhosis. As a final step, the transplant surgeon carefully explores the abdominal cavity for metastases before proceeding. Occasionally a back-up potential recipient will be brought to the transplant center in case metastases are found so that the organ can be given to another patient.

Hepatocellular carcinoma may present as a mass lesion that is found either because of symptoms or as an incidental lesion identified after transplantation by the pathologist in the explant. These incidental tumors are small, typically 3 cm or less in diameter. Patients with incidental hepatic carcinoma have a survival rate that is no different after the procedure from that of patients with cirrhosis alone. In the University of Pittsburgh series, the mean survival of patients undergoing transplantation who had malignant lesions smaller than 2 cm was 76.4 months versus 40.4 months for those with tumors larger than 2 cm.[38]

Data from several transplant centers indicate that several risk factors predict recurrent hepatocellular carcinoma. These include lymph node involvement, gross vascular invasion as seen by angiography or CT scan, microscopic invasion of blood vessels in the specimen, tumor size greater than 5 cm, multiple lesions, the presence of an infiltrating rather than a circumscribed lesion, and involvement of more than one lobe.[38,39] In a recent study of tumor doubling time of recurrent hepatocellular carcinoma after transplantation and after hepatic resection, tumors grew at a significantly faster rate when they recurred after transplantation.[40] This accelerated growth rate may be related to the consequences of immunosuppression with inhibition of host immunity against micrometastases.[40]

The likelihood of tumor recurrence after transplantation has led researchers to analyze the role of partial or subtotal hepatic resection compared with transplantation. Retrospective-analysis of data from patients with hepatocellular carcinoma who underwent either hepatic resection or transplantation showed similar survival rates of as long as five years. The key factor in predicting recurrence was the tumor-node-metastasis (TNM) staging. Patients with cirrhosis had better survival after transplantation than after resection because considerable hepatic morbidity and mortality were associated with the resection of lesions in a cirrhotic liver. Patients with fibrolamellar disease and early tumor stages had the best survival.

The one- to five-year survival rates of patients receiving transplants for primary hepatic carcinoma at selected large transplant centers are displayed in Table 1.[38,39,41-43] The three- and five-year survival rates vary from approximately 15% to 40%. Selection factors appear to be critical, and improved survival can be predicted by standard TNM staging.[38,39] A particular problem for patients with hepatocellular carcinoma is difficulty in procuring a donor liver quickly based on the current policies of the United Network for Organ Sharing, which allocates liv-

TABLE 1.—*Survival After Orthotopic Liver Transplantation for Hepatocellular Carcinoma at Representative Large Liver Transplant Centers*

Center	Reference	Patients, No.	Survival, % 1-yr	2-yr	3-yr	5-yr
University of Pittsburgh	Iwatsuki et al[38]	105	65.7	49.0	39.2	35.6
Medizinische Hochschule	Ringe et al[39]	61	37.7	26.7	15.2	15.2
King's College Hospital	O'Grady et al[41]	50	42.5* 48.5†	37.3* 38.3†	--	--
New England Deaconess	Haug et al[42]	24	71.0	56.0	42.0	--
University of California, Los Angeles	Olthoff et al[43]	16	40.4	22.5	--	--

*Patients with hepatocellular carcinoma and cirrhosis.
†Patients with hepatocellular carcinoma but no cirrhosis.

ers to patients who are most ill with liver failure and have been on the waiting list the longest. Patients with hepatocellular carcinoma may need to wait six months or longer for a transplant.

Several adjuvant therapies are available for hepatic carcinoma, particularly when the tumors are small and few in number.[44] These therapies, including doxorubicin hydrochloride given before, during, or after the procedure[45] and pretransplantation chemoembolization—selective embolization of the feeding artery with gelatin sponge particles soaked in solutions of doxorubicin, mitomycin, and cisplatin[46]—show promise in improving the results of liver transplantation alone for hepatocellular carcinoma.

In summary, the optimal treatment of primary hepatic carcinoma would appear to be partial hepatic resection if a single tumor is present in a noncirrhotic liver in a location amenable to safe resection. The only option for patients with tumors unresectable by conventional surgical techniques and hepatocellular carcinoma that occurs with cirrhosis and poor hepatic function is orthotopic liver transplantation. Long-term survival is only 20% to 30%, which mandates that only patients having a favorable TNM staging and receiving some form of adjuvant chemotherapy should undergo the procedure.

Older Age and Liver Transplantation

Until the early 1980s, the usual accepted age limit for liver transplant candidates was 50 years. Although a report of US liver transplant survival data suggests that older patients have reduced survival,[47] analysis of data from nearly all large centers does not support this general conclusion. Data compiled over the past several years from the University of Pittsburgh show that patients older than 60 account for almost 11% of patients receiving transplants.[48] The survival of this group of patients, which included 156 recipients, is virtually identical with the survival of adults younger than 60.[48] Most of these older patients recovered fully with good functional status and without major symptoms. Of the survivors, 66.7% were fully functional and 27.3% were functional with some limitation; only 6% were partially or completely disabled.[48] The number of patients older than 60 years undergoing liver transplantation is increasing out of proportion to the number of younger patients receiving transplants. The approval of Medicare funding for the procedure should further increase the percentage of patients older than 60 years who have transplantation.

Data from the University of Nebraska are similar to those from the University of Pittsburgh and demonstrate that survival in patients older than 60 is the same as for those younger than 60.[49] When investigators in Nebraska analyzed their older patients according to their risk of dying of liver disease,[50] some important findings were seen in their senior recipients. Low-risk older patients had a survival rate that was essentially identical to that of younger adults—17 of 18 patients.[49] On the other hand, among 15 older patients who were at medium risk, one-year survival dropped to 60%. Those elderly patients who were at highest risk had only 30% one-year survival. These findings suggest that medically high-risk older patients might be excluded from transplantation, even though a small percentage had good survival.

The results of transplantation at the University of Wisconsin Medical Center in patients older than 60 years are also encouraging. The actuarial survival was 83% at two years, compared with 76% for recipients younger than 60 years.[51] At CPMC, the actuarial survival of 38 patients

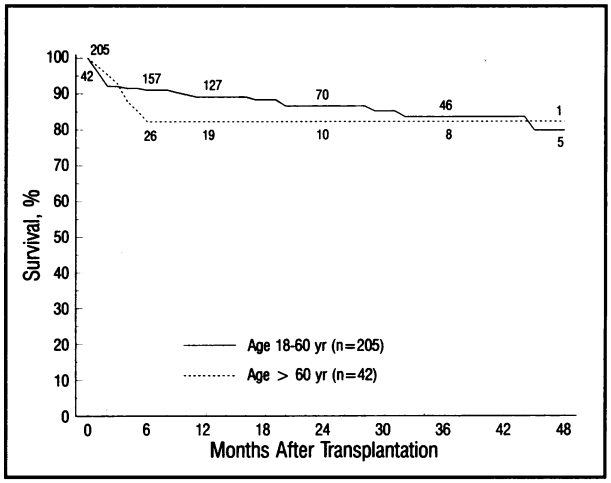

Figure 3.—The actuarial survival of patients older than 60 years who undergo transplantation is similar to that of adults between ages 18 and 60 receiving transplants.

older than 60 years is not different from the survival of all other adult patients (Figure 3). Thus, results from several centers demonstrate that older subjects generally do well after transplantation.

The incidence of acute rejection may be lower in older patients, and age itself may induce a degree of immunosuppression that explains the lower incidence of rejection.[48] Lower doses of immunosuppressive drugs may be appropriate in the elderly. In particular, the dosage of corticosteroids should be minimized to reduce the risk of problems such as diabetes mellitus, cataracts, and osteopenia.

In summary, survival rates after liver transplantation for patients older than age 60 are not different at one or three years from those of younger adults undergoing the same procedure. These results likely reflect the stringent selection and evaluation process that identifies older patients free of cardiac, pulmonary, and vascular disease. The primary concern in patient selection among the elderly is high-risk patients with advanced liver disease, who have poor survival. Thus, early referral is even more important in this age group.

Conclusions

Our recommendations regarding orthotopic liver transplantation for the controversial patient indications reviewed are as follows:

- Alcoholic liver disease: Offer transplantation to patients with good prognostic factors for sobriety and compliance;
- Chronic hepatitis B: Transplantation only in the setting of an experimental protocol, such as HBIG therapy that shows promise in reducing HBV reinfection, and possibly only for patients who are HBeAg- and HBV DNA-negative;
- Primary liver cancer: Offer the procedure only for the few patients who cannot have their hepatocellular carcinoma resected, have favorable TNM staging, and participate in an experimental protocol such as adjuvant chemotherapy or chemoembolization; and
- Patients older than age 60: Transplantation is acceptable, except possibly excluding high-risk patients with far advanced liver disease who have substantially reduced survival.

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* * *

STROKE

Furious, frantic, downed as a flash-flooded
oak, her left hand didn't wither, but dropped
in a second all its green leaves,
her left leg shriveled to a seeming-useless wire,
worthless as a severed root—

hope dried like cracked vines in an old, old
Italian garden, crookedly weaving between toppled
statues of children, young women, staring
at dirt, not daring to wish for rain, wind
or the next day, or any day—

but pith-deep in this woman, iron, water
mixed to explode, pushed sap back through
kinked, flaking canals of brain,
refueled stuttering cell fires—

and after weeks of sun and dark,
low-banked steady fury,
her hand undulates in the light,
she steps again with a walker down the street.

RON LINDER, MD©
San Francisco, California